GG of rs2910164 (miR-146a) (P<0.01). Cox regression analysis showed that the miR-146aC>G polymorphism was associated with serious prognosis of CAD.
Conclusions: The miR-146aG allele is associated with pathogenesis and prognosis of CAD, especially for AMI patients.
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GW25-e5416

3-Bromopyruvate prevents monocrotaline-induced pulmonary arterial hypertension in rats

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Objectives: Pulmonary arterial hypertension (PAH), which is characterized by a progressive elevation of pulmonary vascular resistance and leads to right heart failure and even death. Basis of the "Warburg effect", the metabolism shifts from oxidative mitochondria to glycolysis and the elevated enzyme hexokinase-2 (HK2) in PAH. An inhibitor of HK2, 3-bromopyruvate (3-BrPA), promptly and substantially suppresses ATP and lactic acid, however, it could prevents the development of PAH is not yet known.
Methods: Sprague-Dawley rats with monocrotaline (MCT, 60 mg/kg) -induced PAH were administered subcutaneous injection of 3-BrPA (7.5mg/kg/d, 15mg/kg/d and 30mg/kg/d, respectively) for 14 days. Hemodynamic parameters were acquired by right heart catheterization. Histopathology, immunohistochemisty, and assessments of relative enzyme expressions were performed in rat lung tissue.
Results: Compared with MCT rats, 3-BrPA significantly decreased mean pulmonary arterial pressure; pulmonary vascular resistance (PVR) and right heart hypertrophy (RVH), and increased cardiac output. In additional, 3-BrPA treatment markedly reduced MCT-induced increase in both the wall thickness and area. 3-BrPA significantly suppressed proliferation and enhanced apoptosis of pulmonary artery smooth muscle cells, attenuating small pulmonary artery remodeling. Furthermore, treatment with 3-BrPA significantly increased endothelial NO synthase expression, cytochrome c in cytoplasm and superoxide dismutase activity, and down-regulated HK2 expression and ATP production.
Conclusions: These investigations demonstrated the importance of glycolytic inhibition in PAH pathogenesis and highlight 3-BrPA may beneficial to the therapy of PAH.

GW25-e0008

Cortistatin protects myocardium from endoplasmic reticulum stress induced apoptosis during sepsis

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Objectives: Sepsis is generally viewed as a disease aggravated by a systemic inflammatory response to infection. Myocardial depression is a well-recognized manifestation of organ dysfunction in sepsis, and myocardial apoptosis is a key step for this progression. Cortistatin (CST), a cyclic neuropeptide related to somatostatin, prevents septic shock-associated lung and liver injury, and improves survival in experimental sepsis. However, the effect of CST on myocardium remains unclear. This study aimed to assess whether CST protects the myocardium from sepsis-induced apoptosis.
Methods: To test that, the murine model of cecal ligation and puncture (CLP) and LPS induced cardiomyocytes (CM) were used in vitro. To measure rat CST and its receptors mRNA levels, we used real-time PCR. Electron microscopy, TUNEL staining, caspase-3 activity and Bcl-2/Bax ratio were used to determine myocardial apoptosis. Western-blot was used to test endoplasmic reticulum stress markers, such as GRP94, caspase-12 and CHOP.
Results: Compared with the sepsis-alone group, rats under CST treatment showed higher MABP, by 37.8%. And CST elevated values of +LVdp/dtmax by 54.1%, and LVdp/dtmax by 48.3%, and LVSP by 27.5%. We further confirmed that by using TUNEL staining and caspase-3 activity assay, and showed there is a significant decrease of cardiomyocytes apoptosis after CST pretreatment. On Western blot analysis, compared with sepsis group the ratio of Bcl-2/Bax increased by 2.6-fold in the CST+sepsis group (P<0.05). We further investigated the expression of ERS marker: the protein levels of GRP94, caspase-12, CHOP were about 2.7-fold, 9.2-fold, 6.2-fold (all P<0.05) higher, respectively, in sepsis than control myocardium; however, the upregulated expression of these proteins was downregulated with CST treatment, by 52.8%, 29.5%, 36.6% (all P<0.05) respectively. In vitro, we also found that CST treatment significantly decrease LPS induced these molecules expression. To further investigate the direct inhibitory effect of CST on ERS in vitro, we used DTT to induce cardiomyocytes. The protein levels of ERS markers were significantly increased after chemicals incubation for 3h. Preincubation with cortistatin abolished the increased levels of ERS markers. We found that D-GHRP-6, GHS-R1a antagonist completely blocked cortistatin's inhibitory effect on cardiomyocyte ERS, indicating CST inhibit ERS through GHS-R1a.
Conclusions: In conclusion, CST pretreatment attenuated sepsis induced depressed cardiac function and apoptosis and inhibited the overexpression of ERS markers. In vitro, CST directly inhibited ERS, which might depend on GHS-R1a. For the first time, we show that CST protects heart against sepsis injury and apoptosis, at least partially through its inhibitory effect on myocardial ERS and through activation its receptor GHS-R1a, which may provide a new insight into the mechanism underlying the wide cardiovascular protective actions of CST atin.

GW25-e0051

Suppression of cardiac TFEB sumoylation promotes age-associated reduction in autophagy

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Objectives: Aging-dependent decline of autophagy contributes to cardiac dysfunction and ischemic intolerance. Transcription factor EB (TFEB) is a master transcriptional regulator of the autophagy-lysosome pathway. The present study aimed to characterize the role of TFEB in the autophagic decrease with aging.
Methods: We analyzed age-associated autophagic changes in male C57BL/6 young (4-6 mo) and aged (22-24 mo) mice.
Results: The results demonstrated that TFEB expressed predominantly as a SUMOylated form in cardiomyocyte nuclei and this SUMOylation of TFEB declined in aged heart associated with autophagy reduction. Interestingly, SUMOylation of TFEB was unaffected by rapamycin. Rapamycin induced translocation of TFEB into nucleus but lower level of nuclear TFEB in aged hearts than that seen in young hearts (P<0.05). SUMO1 downregulation by adeno-associated-virus-mediated small hairpin RNA (rAAV9-shSUMO1) significantly reduced nuclear TFEB levels (P<0.05), depressed cardiac autophagy and accelerated cardiomyocyte contractile dysfunction with worse hypoxia/reoxygenation (H/R) injury (all P<0.05). Therefore, impaired SUMOylation decreased nuclear TFEB during aging. By contrast, SUMO1 restitution significantly augmented nuclear SUMOylated TFEB with enhanced autophagy and ultimately reduced infarct size in aged heart. However, knockdown of cardiac TFEB blocked the protective effect of upregulation of SUMO1 in aged hearts, resulted in decline of autophagy and worse *in vivo* I/R injury.
Conclusions: The present study newly demonstrates that SUMOylation is a critical post-translational modification that regulates cardiac TFEB. Impaired SUMOylation of TFEB aggravates decline of autophagy in the senescent heart. Targeting SUMO1 may provide a novel therapeutic strategy for the treatment of aging-related loss of cardioprotection.

GW25-e0306

Effect of Xiongdan on Blood Pressure, Mesenteric Vascular Structure and Function in Spontaneously Hypertensive Rats

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Objectives: To observe the effect of Xiongdan on blood pressure, vascular structure and dilatation function of 3rd grade branch mesenteric arteries in spontaneously hypertensive rats (SHRs).
Methods: Sixteen male SHRs at 12 wks old were randomly divided into 2 groups: Xiongdan (SHR-X, n=8, a traditional Chinese herbal compound, 800mg·kg^{-1}·d^{-1}) and untreated controls (SHR, n=8). Age- and weight-matched WKY rats served as controls (WKY, n=8). Systolic blood pressure (SBP) was measured by tail-cuff method before treatment, 4 and 8 wks after treatment. The wall-to-lumen area ratios (W/L), the ratios of wall thickness (WT) to lumen radius (LR) of 3rd grade branch mesenteric arteries were assessed morphometrically. Endothelium-dependent relaxation (EDdR), endothelium-independent relaxation (EDiR) was measured by PowerLab biological signal analytical system.
Results: SBP in SHRs were higher than that in WKY from 12 to 20 wks. SBP in X treated rats was significantly lower than that in untreated rats [SBP/mmHg, 4wks: SHR-X 176.45±11.44 vs SHR 200.27±13.94; 8wks: SHR-X 169.43±11.97 vs SHR 189.88±10.06, both P<0.01]. W/L and WT/LR of 3rd grade branch mesenteric arteries in X treated rats were markedly lower than that of untreated SHR [W/L: SHR-X 0.53±0.09 vs SHR 1.82±0.96; WT/LR: SHR-X 0.24±0.08 vs SHR 0.53±0.29, both P<0.01], similar to the level as that of WKY (P>0.05). Compared with SHR, EDdR [Emax/%: SHR-X 59.29±15.15 vs SHR: 20.69±6.31, pD_2 : SHR-X 8.24±0.13 vs SHR 5.82±0.23; both P <0.01] and EDiR [Emax/%: SHR-X 96.37±1.87 vs SHR 29.04±4.56, pD_2: SHR-X 7.79±0.15 vs SHR 5.31±0. 14; both P<0.01] of 3rd grade branch mesenteric arteries were increased in X treated after 8wks treatment.
Conclusions: The treatment of Xiongdan may lower blood pressure, ameliorate the vascular structure and dilatation function of 3rd grade branch mesenteric arteries in SHRs.

GW25-e0419

Prenatal Lipopolysaccharide Exposure Results in Dysfunction of Renal Dopamine D1 Receptor in Offspring Rats

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Objectives: Adverse environmental exposure in utero predisposes to adult disease, including hypertension. Exposure to lipopolysaccharide (LPS) results in increased blood pressure in offspring, but the exact mechanisms are not clear. Our previous study shows dysfunction of renal D1 receptor (D1R) is ascribed to the pathogenesis of hypertension, which is associated with reactive oxidative stress (ROS). In this study, we test whether dysfunction of renal D1R is involved in fetal programmed hypertension, and whether oxidative stress contributes to this process.